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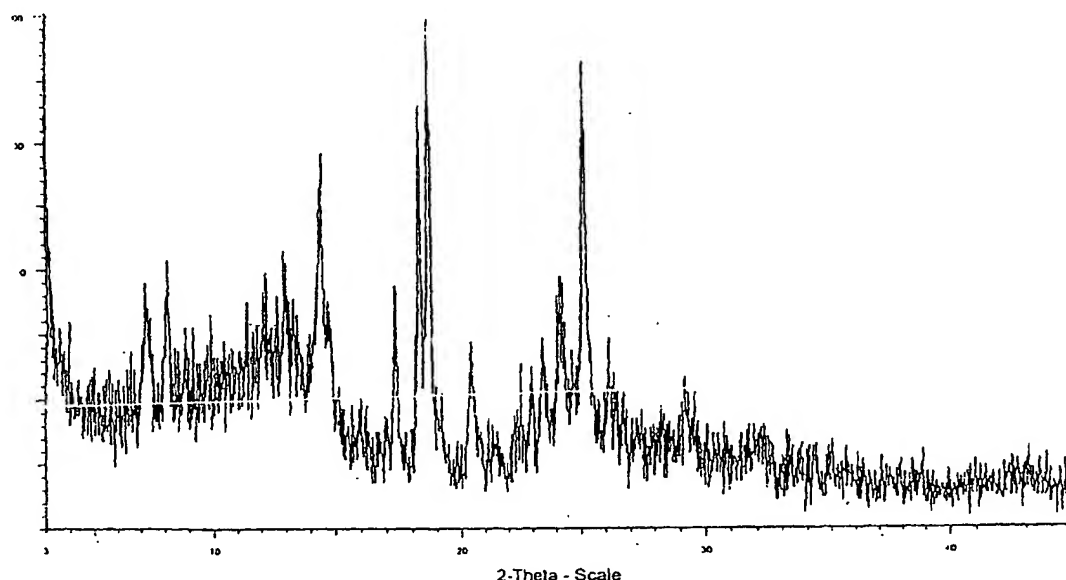
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(54) Title: **CRYSTALLINE [2-[4-[(4-CHLOROPHENYL)-PHENYL METHYL]-1-PIPERAZINYL] ETHOXY] ACETIC ACID DIHYDROCHLORIDE**



(57) Abstract: A crystalline form of cetirizine dihydrochloride is provided. A Form I of cetirizine dihydrochloride having a defined X-ray diffraction pattern is also provided, as well as pharmaceutical compositions containing the same.

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Crystalline [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid
dihydrochloride

FIELD OF THE INVENTION

The present invention relates to a crystalline form of [2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid dihydrochloride, which is generically known as cetirizine dihydrochloride.

BACKGROUND OF THE INVENTION

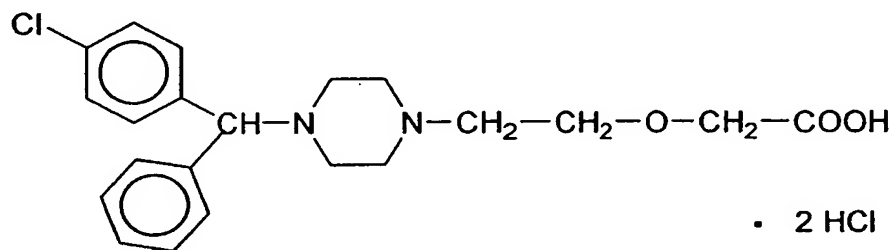
Cetirizine dihydrochloride is orally active, long-acting histamine H₁ receptor antagonist. It belongs to the second generation of H₁ histamine receptor antagonists that are thought to offer some significant advantages over the first generation compounds. The advantages are believed to include less sedation, low anticholinergic activity, and longer acting duration with the resulting improves patient compliance. Cetirizine is used for the treatment of allergic syndromes, such as chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria, and the like.

The preparation of cetirizine generally is known in the art. For example, the process for the preparation of cetirizine and its salts is disclosed U.S. Patent No. 4,525,358. The disclosed process involves hydrolysis of the methyl ester of cetirizine using ethanolic potassium hydroxide to afford potassium salt of cetirizine. The solution containing the potassium salt is then acidified with hydrochloric acid. U.S. Patent No. 6, 255, 487 discloses a process for the preparation of cetirizine dihydrochloride via condensation of (4-chloro

phenyl) phenyl methyl chloride and potassium 2-(1-piperazinyl) ethoxyacetate in acetonitrile, followed by acidification in acetone medium with concentrated hydrochloric acid.

SUMMARY OF INVENTION

For some drugs, amorphous and crystalline forms exhibit different dissolution characteristics, and, in some cases, different bioavailability patterns. *See, e.g., Konne T., Chem. Pharm. Bull.* 38, 2003 (1990), incorporated herein by reference. Furthermore, for certain indications, one bioavailability pattern may be favored over another. It is believed that preparation of crystalline cetirizine dihydrochloride is not known in the art. Thus, it was recognized that it might be desirable to obtain a crystalline form of cetirizine dihydrochloride:



In accordance with one aspect, the invention provides a crystalline form of cetirizine dihydrochloride. Preferably, the crystalline form of cetirizine dihydrochloride has an X-ray diffraction pattern obtained with a diffractometer equipped with a copper K X-radiation source and expressed in terms of 2 theta angles, wherein the X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10±0.09, 8.01±0.09, 8.76±0.09, 12.59±0.09, 12.97±0.09, 13.53±0.09, 14.42±0.09, 14.73±0.09, 15.92±0.09, 16.68±0.09, 16.96±0.09, 17.33±0.09, 18.24±0.09, 18.64±0.09, 20.39±0.09, 22.95±0.09, 23.43±0.09, 24.14±0.09, 25.12±0.09, 26.11±0.09, 26.71±0.09, 29.20±0.09, 33.80±0.09, 34.34±0.09, 35.04±0.09, and 43.15±0.09. More

preferred crystalline form of cetirizine dihydrochloride has an X-ray diffraction pattern with the following peaks: 7.099, 8.007, 8.756, 12.592, 12.966, 13.526, 14.423, 14.731, 15.923, 16.676, 16.965, 17.328, 18.244, 18.637, 20.388, 22.949, 23.432, 24.143, 25.115, 26.109, 26.706, 29.204, 33.796, 34.342, 35.044 and 43.147. Yet more preferably, the crystalline form of cetirizine dihydrochloride has substantially the same X-ray diffraction pattern as shown in Figure 1.

In accordance with another aspect, the invention provides a pharmaceutical composition that includes a prophylactically or therapeutically effective amount of the crystalline form of cetirizine dihydrochloride and one or more pharmaceutically acceptable excipients. Preferably, the pharmaceutical composition includes the crystalline form of cetirizine dihydrochloride that has an X-ray diffraction pattern obtained with a diffractometer equipped with a copper K X-radiation source and expressed in terms of 2 theta angles and, wherein the X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10 ± 0.09 , 8.01 ± 0.09 , 8.76 ± 0.09 , 12.59 ± 0.09 , 12.97 ± 0.09 , 13.53 ± 0.09 , 14.42 ± 0.09 , 14.73 ± 0.09 , 15.92 ± 0.09 , 16.68 ± 0.09 , 16.96 ± 0.09 , 17.33 ± 0.09 , 18.24 ± 0.09 , 18.64 ± 0.09 , 20.39 ± 0.09 , 22.95 ± 0.09 , 23.43 ± 0.09 , 24.14 ± 0.09 , 25.12 ± 0.09 , 26.11 ± 0.09 , 26.71 ± 0.09 , 29.20 ± 0.09 , 33.80 ± 0.09 , 34.34 ± 0.09 , 35.04 ± 0.09 , and 43.15 ± 0.09 . The pharmaceutical compositions of this aspect of the invention may be formulated, for example, as solid dosage forms for oral administration.

In accordance with another aspect, the invention provides a process for preparation of a crystalline form of cetirizine dihydrochloride that includes a) providing a free base or a salt of 2-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid as a solution in an organic solvent; b) treating the solution with hydrochloric acid contained in

an alcoholic solvent, wherein the hydrochloric acid is present in an amount sufficient to form a di-hydrochloric acid salt of 2-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid which separates as a solid mass; and c) isolating the solid mass to obtain the crystalline form of cetirizine dihydrochloride. Pharmaceutical compositions that include a prophylactically or therapeutically effective amount of the crystalline form of cetirizine dihydrochloride produced by the process described, and one or more pharmaceutically acceptable excipients are also provided.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the X-ray powder diffraction of crystalline Form-I of cetirizine dihydrochloride.

Figure 2 is differential scanning calorimetry thermogram of crystalline Form-I of cetirizine dihydrochloride.

Figure 3 is Infrared spectrum of crystalline Form-I of cetirizine dihydrochloride.

DETAILED DESCRIPTION OF THE INVENTION

According to one aspect, the invention provides a crystalline form of cetirizine hydrochloride. The specific crystalline form obtained by the inventors is designated as Form-I. Crystalline Form I of cetirizine dihydrochloride may be prepared, for example, by converting cetirizine free base or a salt of cetirizine to the dihydrochloride with *in situ* crystallization. For example, the process may involve providing a solution of cetirizine base or a salt of cetirizine in an organic solvent; adding alcoholic hydrochloric acid solution;

stirring the solution until separation of a solid mass of cetirizine dihydrochloride; and isolating and drying the product. Ester solvents, such as methyl acetate, ethyl acetate, tertiary butyl acetate, isopropyl acetate, isobutyl acetate and mixture thereof, are preferred for dissolving the starting cetirizine, while the preferred solvent carrier for hydrochloric acid is isopropanol. Preferably, the resulting crystalline cetirizine dihydrochloride is dried at a temperature of from about 40 °C to about 100 °C. The chemical synthesis of starting free base or salt cetirizine may be affected by any method known in the art. For example, the synthesis described in U.S. Pat. No. 4,525,358 cited above and incorporated by reference herein in its entirety, may be used for this purpose.

The crystalline Form I of cetirizine dihydrochloride may be characterized by X-ray diffraction. The X-ray diffraction patterns are unique for the particular crystalline form. Each crystalline form exhibits a diffraction pattern with a unique set of diffraction peaks that can be expressed in 2 theta angles, d-spacing values and relative peak intensities. 2 Theta diffraction angles and corresponding d-spacing values account for positions of various peaks in the X-ray powder diffraction pattern. D-spacing values are calculated with observed 2 theta angles and copper K(α 1) wavelength using the Bragg equation well known to those of skill in the art.

However, slight variations in observed 2 theta angles or d-spacing values are expected based on the specific diffractometer employed the analyst and the sample preparation technique. More variation is expected for the relative peak intensities. Identification of the exact crystal form of a compound should be based primarily on observed 2 theta angles with lesser importance attributed to relative peak intensities.

FIG. 1 shows an X-ray powder diffraction pattern of the crystalline Form I of cetirizine dihydrochloride obtained on a Bruker Axs, D8 Advance Powder X-ray Diffractometer with Cu K alpha-1 Radiation source. The X-ray diffraction pattern for Form 1 of crystalline cetirizine dihydrochloride is shown in Table 1:

| 2-Theta Value (°) | Intensity, I/I₀ (%) |
|------------------------------|---|
| 18.637 | 100.0 |
| 18.244 | 81.1 |
| 25.115 | 78.8 |
| 14.423 | 47.9 |
| 17.328 | 35.9 |
| 8.007 | 28.0 |
| 20.388 | 27.8 |
| 24.143 | 25.8 |
| 7.099 | 25.4 |
| 14.731 | 22.5 |
| 23.432 | 20.7 |
| 12.966 | 20.9 |
| 22.949 | 17.8 |
| 26.109 | 16.5 |
| 29.204 | 11.3 |
| 26.706 | 10.7 |

| | |
|--------|-----|
| 8.756 | 9.9 |
| 19.965 | 9.0 |
| 15.923 | 8.8 |
| 13.526 | 8.5 |
| 33.796 | 7.3 |
| 34.342 | 7.3 |
| 12.592 | 7.0 |
| 35.044 | 6.0 |
| 16.676 | 5.1 |
| 43.147 | 4.8 |

Some margin of error is present in each of the 2 theta angle assignments and d-spacings reported herein. The assigned margin of error in the 2 theta angles for Form I of cetirizine dihydrochloride is approximately ± 0.09 for each of the peak assignments. In view of the assigned margin of error, the crystalline form of cetirizine dihydrochloride of the invention may be characterized by an X-ray powder diffraction pattern that includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10 ± 0.09 , 8.01 ± 0.09 , 8.76 ± 0.09 , 12.59 ± 0.09 , 12.97 ± 0.09 , 13.53 ± 0.09 , 14.42 ± 0.09 , 14.73 ± 0.09 , 15.92 ± 0.09 , 16.68 ± 0.09 , 16.96 ± 0.09 , 17.33 ± 0.09 , 18.24 ± 0.09 , 18.64 ± 0.09 , 20.39 ± 0.09 , 22.95 ± 0.09 , 23.43 ± 0.09 , 24.14 ± 0.09 , 25.12 ± 0.09 , 26.11 ± 0.09 , 26.71 ± 0.09 , 29.20 ± 0.09 , 33.80 ± 0.09 , 34.34 ± 0.09 , 35.04 ± 0.09 , and 43.15 ± 0.09 .

Since some margin of error is possible in the assignment of 2 theta angles and d-spacings, the preferred method of comparing X-ray powder diffraction patterns in order to

identify a particular crystalline form is to overlay the X-ray powder diffraction pattern of the unknown form over the X-ray powder diffraction pattern of a known form. For example, one skilled in the art can overlay an X-ray powder diffraction pattern of an unidentified crystalline form of cetirizine dihydrochloride obtained using the methods described herein, over FIG. 1 and readily determine whether the X-ray diffraction pattern of the unidentified form is substantially the same as the X-ray powder diffraction pattern of Form I. If the X-ray powder diffraction pattern is substantially the same as FIG. 1, the previously unknown crystalline form can be readily and accurately identified as Form I. Although 2 theta angles or d-spacing values are the primary methods of identifying the crystalline form, it may be desirable to also compare relative peak intensities. As noted above, relative peak intensities may vary depending upon the specific diffractometer employed and the analyst's sample preparation technique. The peak intensities are reported as intensities relative to the peak intensity of the strongest peak.

The crystalline form of cetirizine dihydrochloride may be also characterized by differential scanning calorimetry and/or infrared spectroscopy. The DSC thermogram of crystalline Form I of cetirizine dihydrochloride obtained by the inventors is shown in FIG. 2. It exhibits a significant endo-endo pattern with identified peaks around 186°C and 205°C. It was measured on Shimadzu differential scanning calorimeter in a temperature range of 50-250°C with a heating rate of 5°C/minute. The infrared spectrum of crystalline Form I of cetirizine dihydrochloride obtained by the inventors is shown in FIG. 4. It was measured on Perkin-Elmer FT-IR instrument by KBr-transmission method. The significant bands may be identified at approximately 3413, 2947, 2422, 1742, 1494, 1319, 1137, 919 and 700 cm⁻¹.

Crystalline cetirizine dihydrochloride described herein, including Form I, may be used as an active ingredient in pharmaceutical formulations. The pharmaceutical compositions of the invention contain cetirizine dihydrochloride as the active ingredient, and one or more pharmaceutically acceptable excipients. Suitable pharmaceutically acceptable excipients include starches, sugars, celluloses, such as microcrystalline cellulose, hydroxypropyl cellulose, and hydroxypropylmethyl cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like. Generally, the pharmaceutical compositions of the present invention are prepared by uniformly admixing the active ingredient with liquid or solid carriers and then shaping the product into the desired form. The pharmaceutical compositions may be in the form of suspensions, solutions, elixirs, aerosols, or solid dosage forms. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. Examples of formulations suitable for crystalline cetirizine dihydrochloride of the invention are disclosed in U.S. Patents Nos. 6,245,353 and 5,698,558, the disclosures of which are incorporated herein by reference in their entirety.

The more preferred oral solid preparation is a tablet. A tablet may be prepared by direct compression, wet granulation, or molding, of the crystalline cetirizine dihydrochloride with a carrier and other excipients in a manner known to those skilled in the art. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active agent or dispersing agent. Molded tablets may be made on a suitable machine, a mixture of the powdered compound moistened with an inert liquid diluent. are suitable in the case of oral solid dosage forms (*e.g.*, powders, capsules, and tablets). If desired,

tablets may be coated by standard techniques. The crystalline cetirizine dihydrochloride described herein may be formulated into typical disintegrating tablet, or into a controlled or extended release dosage forms. Examples of suitable controlled release formulation vehicles are disclosed in U.S. Patents Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123; and 4,008,719, the disclosures of which are hereby incorporated by reference in their entirety. Preferably, each tablet contains from about 2 mg to about 10 mg of the crystalline cetirizine dihydrochloride, and each cachet or capsule contains from about 2 mg to about 10 mg of the crystalline cetirizine dihydrochloride. Most preferably, the tablet contains about 2 mg, about 5 mg or about 10 mg of the crystalline cetirizine dihydrochloride for oral administration.

The prophylactic or therapeutic dose of crystalline cetirizine dihydrochloride will vary with the severity of the condition to be treated and the route of administration. The dose and perhaps the dose frequency will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range for the crystalline cetirizine dihydrochloride is from about 1.0 mg to about 25 mg. Preferably, a daily dose range should be about 2.0 mg to about 20 mg in single or divided doses; most preferably, the dose range is from about 5 mg to about 10 mg per day. It is known that children and elderly patients, as well as those with impaired renal or hepatic function, should receive low doses, at least initially. The term "prophylactically or therapeutically effective amount" refers to the above-described dosage amounts and dose frequency schedules. Any suitable route of administration may be employed. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), and transdermal, and like forms of administration may be suitable. Oral route of administration is preferred.

The invention is further defined by reference to the following examples describing in detail the preparation of the compound and the compositions of the present invention, as well as their utility. It will be apparent to those skilled in the art, that many modifications, both to materials, and methods, may be practiced without departing from the purpose and interest of this invention.

Reference Example. Preparation of Cetirizine.

[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetamide (50 grams) in 6.5%w/v aqueous sodium hydroxide (200 ml) was refluxed till the reaction was substantially completes. Then the reaction mixture was cooled, further diluted with water (300 ml) accompanied by adjusting the pH of the reaction solution around 9.0 with concentrated hydrochloric acid, washed the resulted reaction mass with ethyl acetate. The pH of the separated aqueous layer was further adjusted to 4.0 with concentrated hydrochloric acid and extracted with dichloromethane. Then the combined dichloromethane layer was evaporated under vacuum to get the required Cetirizine base. (43.0 grams).

Example 1. Preparation of crystalline Form I of cetirizine dihydrochloride.

Cetirizine (10.0 grams) was dissolved in ethyl acetate (100 ml) at a temperature of 25-35°C and stirred for 10-15 min. Isopropanolic hydrochloric acid (20 ml) was added till the pH of reaction mass becomes 2.0. The reaction mass was stirred for 1-2 hours to separate the solid. The separated solid was filtered, washed with ethyl acetate (20 ml) , followed by hexane (10 ml) and on subsequent drying at a temperature of 80-100°C to a constant weight resulted the novel crystalline Form-I of Cetirizine dihydrochloride (Weight: 10.2 grams).

Example 2. Soluble granules containing crystalline cetirizine dihydrochloride

Soluble granules containing crystalline cetirizine dihydrochloride may have the following content:

| Ingredient | Content (mg) |
|---|--------------|
| Cetirizine dihydrochloride crystalline Form I | 10 |
| Calcium carbonate | 800 |
| Citric acid | 900 |
| Avicel | 40 |
| Mannitol | 625 |
| Maltodextrin | 15 |
| Aspartame | 3 |
| Aroma | 20 |

Example 3. Dispersible tablet containing crystalline cetirizine dihydrochloride

Dispersible tablet containing crystalline cetirizine dihydrochloride may have the following content:

| Ingredient | Content (mg) |
|---|--------------|
| Cetirizine dihydrochloride crystalline Form I | 10 |
| Calcium carbonate | 500 |
| Polyvinylpyrrolidone | 17 |
| Avicel | 15 |
| Mannitol | 400 |
| Maltodextrin | 15 |
| Aspartame | 3 |
| Aroma | 20 |

Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar

items or matters immediately following it. Except where the context indicates to the contrary, all exemplary values are intended to be fictitious, unrelated to actual entities and are used for purposes of illustration only. Most of the foregoing alternative embodiments are not mutually exclusive, but may be implemented in various combinations. As these and other variations and combinations of the features discussed above can be utilized without departing from the invention as defined by the claims, the foregoing description of the embodiments should be taken by way of illustration rather than by way of limitation of the invention as defined by the appended claims.

What is claimed is:

1. A crystalline form of cetirizine dihydrochloride.
2. A crystalline form of cetirizine dihydrochloride having substantially the same X-ray diffraction pattern as shown in FIG. 1.
3. A crystalline form of cetirizine dihydrochloride having an X-ray diffraction pattern expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a copper K X-radiation source, wherein said X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10 ± 0.09 , 8.01 ± 0.09 , 8.76 ± 0.09 , 12.59 ± 0.09 , 12.97 ± 0.09 , 13.53 ± 0.09 , 14.42 ± 0.09 , 14.73 ± 0.09 , 15.92 ± 0.09 , 16.68 ± 0.09 , 16.96 ± 0.09 , 17.33 ± 0.09 , 18.24 ± 0.09 , 18.64 ± 0.09 , 20.39 ± 0.09 , 22.95 ± 0.09 , 23.43 ± 0.09 , 24.14 ± 0.09 , 25.12 ± 0.09 , 26.11 ± 0.09 , 26.71 ± 0.09 , 29.20 ± 0.09 , 33.80 ± 0.09 , 34.34 ± 0.09 , 35.04 ± 0.09 , and 43.15 ± 0.09 .
4. The crystalline form of cetirizine dihydrochloride of claim 3, wherein said X-ray diffraction pattern includes peaks with 2 theta angles of 7.099, 8.007, 8.756, 12.592, 12.966, 13.526, 14.423, 14.731, 15.923, 16.676, 16.965, 17.328, 18.244, 18.637, 20.388, 22.949, 23.432, 24.143, 25.115, 26.109, 26.706, 29.204, 33.796, 34.342, 35.044 and 43.147.
5. The crystalline form of cetirizine dihydrochloride of claim 1 that has an endo-endo pattern with identified peaks of about 186°C and 205°C in its differential scanning calorimetry thermogram.
6. The crystalline form of cetirizine dihydrochloride of claim 1 having substantially the same differential scanning calorimetry thermogram as shown in FIG. 2.

7. The crystalline form of cetirizine dihydrochloride of claim 1 having an infrared spectrum with identifiable peaks at about 3413, 2947, 2422, 1742, 1494, 1319, 1137, 919 and 700 cm^{-1} .

8. The crystalline form of cetirizine dihydrochloride of claim 1 having substantially the same infrared spectrum as shown in FIG. 3.

9. A pharmaceutical composition comprising a prophylactically or therapeutically effective amount of the crystalline form of cetirizine dihydrochloride of claim 1 and one or more pharmaceutically acceptable excipients.

10. The pharmaceutical composition of claim 9, wherein said crystalline form of cetirizine dihydrochloride has an X-ray diffraction pattern expressed in terms 2 theta angles and obtained with a copper K X-radiation source, wherein said X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10 ± 0.09 , 8.01 ± 0.09 , 8.76 ± 0.09 , 12.59 ± 0.09 , 12.97 ± 0.09 , 13.53 ± 0.09 , 14.42 ± 0.09 , 14.73 ± 0.09 , 15.92 ± 0.09 , 16.68 ± 0.09 , 16.96 ± 0.09 , 17.33 ± 0.09 , 18.24 ± 0.09 , 18.64 ± 0.09 , 20.39 ± 0.09 , 22.95 ± 0.09 , 23.43 ± 0.09 , 24.14 ± 0.09 , 25.12 ± 0.09 , 26.11 ± 0.09 , 26.71 ± 0.09 , 29.20 ± 0.09 , 33.80 ± 0.09 , 34.34 ± 0.09 , 35.04 ± 0.09 , and 43.15 ± 0.09 .

11. The pharmaceutical composition of claim 10 which is a solid dosage form for oral administration.

12. The pharmaceutical composition of claim 11, wherein said solid dosage form is a tablet.

13. A process for preparation of a crystalline form of cetirizine dihydrochloride, said process comprising:

- a) providing a free base or a salt of 2-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid as a solution in an organic solvent;
 - b) treating said solution with hydrochloric acid contained in an alcoholic solvent, wherein the hydrochloric acid is present in an amount sufficient to form a dihydrochloric acid salt of 2-[2-[4-[(4-Chlorophenyl)-phenyl methyl]-1- piperazinyl] ethoxy] acetic acid which separates as a solid mass;
 - c) isolating said solid mass thereby obtaining said crystalline form of cetirizine dihydrochloride.
14. The process of claim 13, further comprising stirring said solution after said treatment with hydrochloric acid until substantially all of said solid mass is separated.
15. The process of claim 14, further comprising removing an unbound solvent from said isolated solid mass to obtain a substantially dry form of said crystalline form of cetirizine dihydrochloride.
16. The process of claim 15, wherein said step of removing said unbound solvent comprises drying said solid mass at a temperature of from about 40 to about 100° C.
17. The process of claim 13, wherein said organic solvent is an ester solvent.
18. The process of claim 17, wherein said ester solvent is selected from the group consisting of methyl acetate, ethyl acetate, tertiary butyl acetate, isopropyl acetate, isobutyl acetate and mixtures thereof.
19. The process of claim 17, wherein said ester solvent is ethyl acetate.
20. The process of claim 13, where said alcoholic solvent is isopropanol.
21. The process of claim 20, wherein said organic solvent is ethyl acetate.

22. The crystalline form of cetirizine dihydrochloride produced in accordance with a process of claim 13.

23. The crystalline form of cetirizine dihydrochloride produced in accordance with a process of claim 21.

24. The crystalline form of cetirizine dihydrochloride produced in accordance with a process of claim 13 and having an X-ray diffraction pattern expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam curved graphite monochromator using copper K X-radiation source, wherein said X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10 ± 0.09 , 8.01 ± 0.09 , 8.76 ± 0.09 , 12.59 ± 0.09 , 12.97 ± 0.09 , 13.53 ± 0.09 , 14.42 ± 0.09 , 14.73 ± 0.09 , 15.92 ± 0.09 , 16.68 ± 0.09 , 16.96 ± 0.09 , 17.33 ± 0.09 , 18.24 ± 0.09 , 18.64 ± 0.09 , 20.39 ± 0.09 , 22.95 ± 0.09 , 23.43 ± 0.09 , 24.14 ± 0.09 , 25.12 ± 0.09 , 26.11 ± 0.09 , 26.71 ± 0.09 , 29.20 ± 0.09 , 33.80 ± 0.09 , 34.34 ± 0.09 , 35.04 ± 0.09 , and 43.15 ± 0.09 .

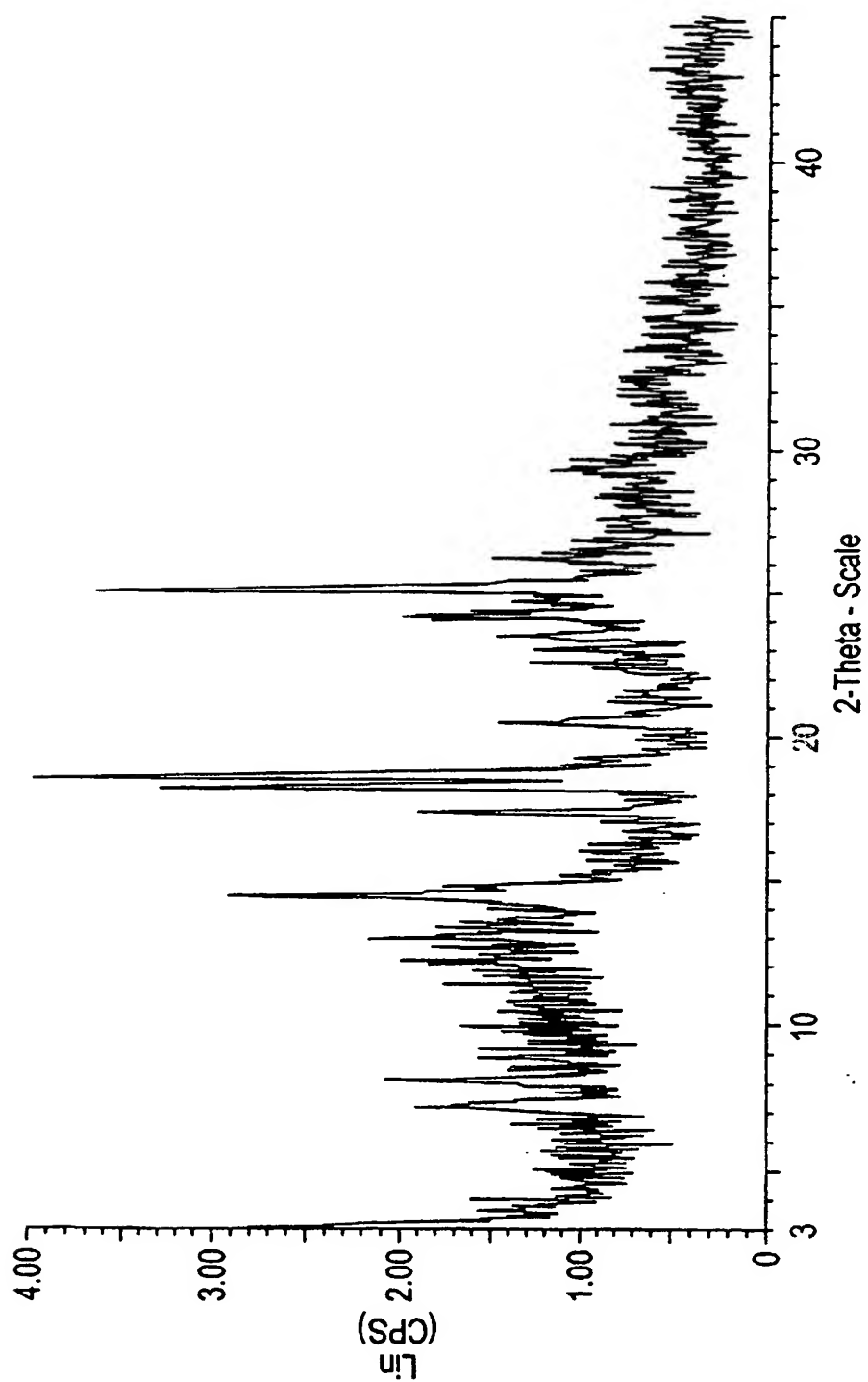
25. A pharmaceutical composition comprising a) a prophylactically or therapeutically effective amount of the crystalline form of cetirizine dihydrochloride produced by the process of claim 13, and b) one or more pharmaceutically acceptable excipients.

26. A pharmaceutical composition comprising a) a prophylactically or therapeutically effective amount of the crystalline form of cetirizine dihydrochloride produced by the process of claim 21 and having an X-ray diffraction pattern expressed in terms 2 theta angles and obtained with a diffractometer equipped with a diffracted beam curved graphite monochromator using copper K X-radiation source, wherein said X-ray powder diffraction pattern includes five or more peaks selected from the group consisting of peaks with 2 theta angles of 7.10 ± 0.09 , 8.01 ± 0.09 , 8.76 ± 0.09 , 12.59 ± 0.09 , 12.97 ± 0.09 , 13.53 ± 0.09 , 14.42 ± 0.09 ,

14.73±0.09, 15.92±0.09, 16.68±0.09, 16.96±0.09, 17.33±0.09, 18.24±0.09, 18.64±0.09, 20.39±0.09, 22.95±0.09, 23.43±0.09, 24.14±0.09, 25.12±0.09, 26.11±0.09, 26.71±0.09, 29.20±0.09, 33.80±0.09, 34.34±0.09, 35.04±0.09, and 43.15±0.09, and b) one or more pharmaceutically acceptable excipients.

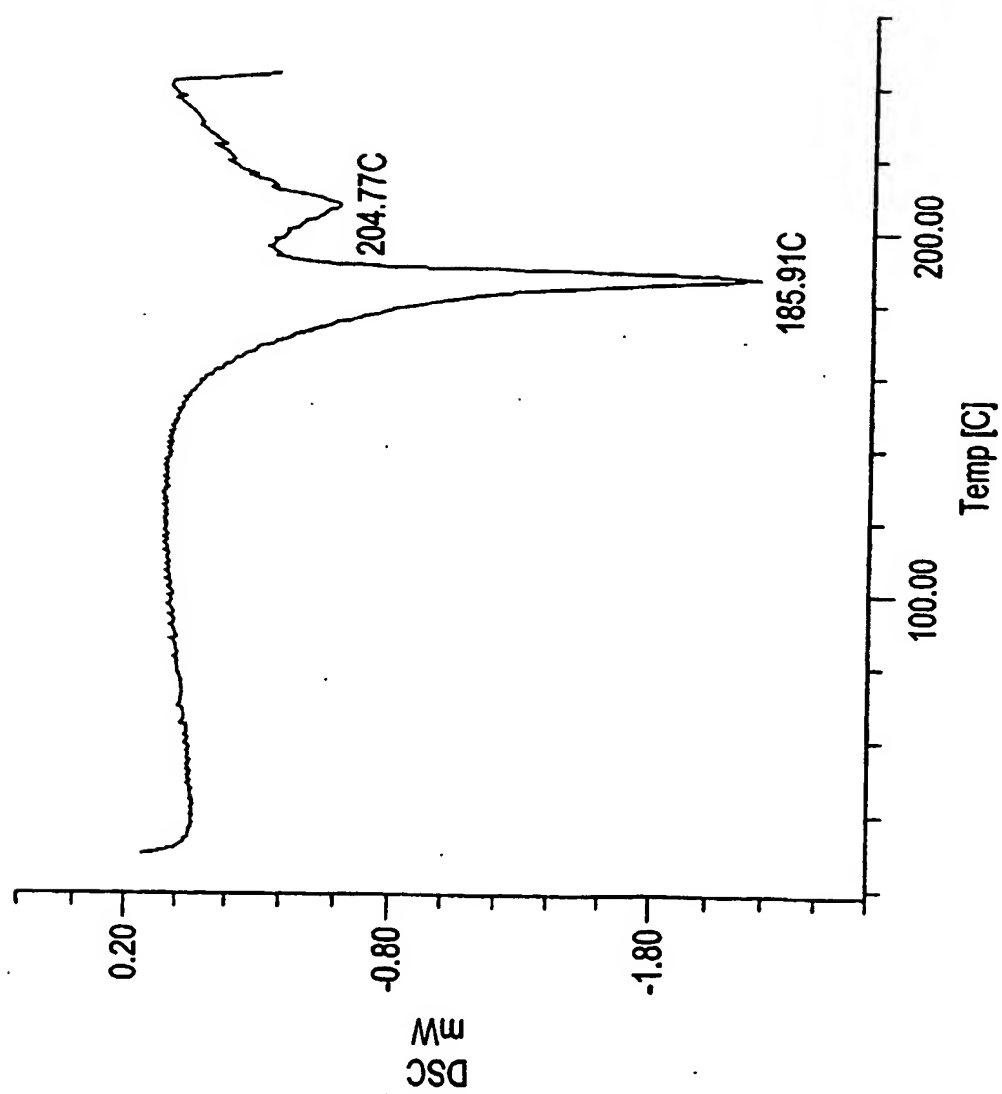
27. The pharmaceutical composition of claim 26, which is a tablet.

FIG. 1



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FIG. 2



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